

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
23 September 2004 (23.09.2004)

PCT

(10) International Publication Number
WO 2004/080461 A2

(51) International Patent Classification: **A61K 31/4545**,
A61P 37/06

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(21) International Application Number:

PCT/US2004/007723

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(22) International Filing Date: 12 March 2004 (12.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/454,299	12 March 2003 (12.03.2003)	US
60/515,354	28 October 2003 (28.10.2003)	US
60/516,904	3 November 2003 (03.11.2003)	US
60/526,339	1 December 2003 (01.12.2003)	US

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: STABLE PHARMACEUTICAL COMPOSITIONS OF DESLORATADINE

(57) Abstract: Provided is a stable pharmaceutical composition of desloratadine.



WO 2004/080461 A2

STABLE PHARMACEUTICAL COMPOSITIONS OF DESLORATADINE**PRIORITY**

- 5 This application claims the benefit of U.S. provisional application Serial No. 60/526,339, filed December 1, 2003, U.S. provisional application Serial No. 60/516,904, filed November 3, 2003, U.S. provisional application Serial No. 60/515,354, filed October 28, 2003, and U.S. provisional application Serial No. 60/454,299, filed March 12, 2003, the contents of all of which are incorporated herein.

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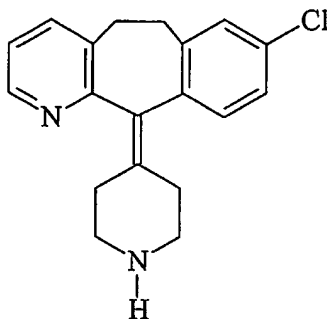
FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions of desloratadine.

BACKGROUND OF THE INVENTION

- 15 Desloratadine, known as 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, has the following structure:

20



- 25 and is disclosed in U.S. Pat. No. 4,659,716. Desloratadine is currently marketed as Clarinex[®] in the United States. Clarinex is prescribed as an antihistamine for prevention or treatment of allergenic reactions, which may result in symptoms such as sneezing, itchy eyes and hives. The '716 patent discloses methods for preparing and administering desloratadine and its pharmaceutically acceptable salts, and is incorporated herein by
30 reference. *See also* U.S. Pat. No. 4,282,233, incorporated herein by reference, which discloses loratadine.

The present invention relates to the solid state physical properties of desloratadine. These properties can be influenced by controlling the conditions under which desloratadine is obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product. When particles of the powdered compound do not flow past each other easily, a formulation specialist must take that fact into account in developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talc, starch or tribasic calcium phosphate.

Another important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's stomach fluid can have therapeutic consequences since it imposes an upper limit on the rate at which an orally-administered active ingredient can reach the patient's bloodstream. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medicaments. The solid state form of a compound may also affect its behavior on compaction and its storage stability.

These practical physical characteristics are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular polymorphic form of a substance. The polymorphic form may give rise to thermal behavior different from that of the amorphous material or another polymorphic form. Thermal behavior is measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) and can be used to distinguish some polymorphic forms from others. A particular polymorphic form may also give rise to distinct spectroscopic properties that may be detectable by powder X-ray crystallography, solid state ^{13}C NMR spectrometry and infrared spectrometry.

In Example V, the '716 patent prepares desloratadine in the solid state and discloses: "Extract the organic material with chloroform, wash with water and remove the solvent. Triturate the residue with hexane. Recrystallize from a large volume of hexane after charcoal decolorization to obtain the product, m.p. 151°-152°C."

In Example VI, B, desloratadine is also prepared in the solid state: "The material is extracted several times with chloroform, the chloroform extracts washed with water and concentrated to dryness, and the residue triturated with petroleum ether or hexane to yield 11.5 grams (93%) m.p. 149°-151°C. After recrystallization from hexane, the product
5 melts at 150°-151°C." The starting material for Example VI, B, is an N-cyano compound prepared according to the disclosure in U.S. Pat. No. 3,326,924.

Both U.S. Pat. No. 4,282,233 and U.S. Pat. No. 3,326,924 are incorporated herein by reference, particularly for their disclosure of preparation of desloratadine.

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U.S. Pat. No. 6,506,767 discloses two polymorphic forms of desloratadine, labelled Forms I and II (*syn.* form 1 and form 2). The XRPD peaks and the FTIR spectrum for the forms are also disclosed in the '767 patent.

15 The '767 patent discloses: "Surprisingly we discovered that certain alcoholic solvents, e.g., hexanol and methanol produced 100% polymorph form 1, but others, e.g., 3-methyl-1-butanol and cyclohexanol produced significant amounts of form 2. Chlorinated solvents, e.g., dichloromethane produced form 1 substantially free of form 2 but the compounds were discolored. Ether solvents such as dioxane produced form 1
20 substantially free of form 2 but other alkane ethers,, e.g., di-isopropyl ether produced form 1 with significant amounts of form 2 and di-n-butyl ether favored formation of form 2. Ketones such as methyl isobutyl ketone produced crystalline polymorph form 1 essentially free of form 2 but methyl butyl ketone produced a 8:1 ratio of form 1 to form 2. Use of methyl isobutyl ketone is preferred to produce crystalline polymorph form 1
25 essentially free of form 2. Only ethyl acetate and di-n-butyl ether were found to produce crystalline polymorph form 2 substantially free of form 1. Use of di-n-butyl ether is preferred for producing crystalline form 2 substantially free of fom 1."

The '767 patent, in Examples 1-3, prepares Form I by crystallization out of methyl isobutyl ketone, while in examples 4 and 5, prepares Form II by crystallization out of
30 ethyl acetate and di-n-butyl ether, respectively.

The '767 patent also carried out stability tests on Polymorph Form I. According to the '767 patent, Form I was "subjected to stability testing at various temperatures (25, 30 and

40°C) and relative humidities of 60%, 60% and 75%, respectively...No significant change (<1%) from initial sample % form I and related compounds was observed.”

The ‘767 patent warns against using polymorphic mixtures of desloratadine for
5 formulation. According to the ‘767 patent, “such a mixture could lead to production of a [desloratadine] which would exist as a variable mixture of variable composition (i.e., variable percent amounts of polymorphs) having variable physical properties, a situation unacceptable in view of stringent GMP requirements.”

10 The ‘767 patent is incorporated herein by reference in its entirety, and more particularly in respect to its characterization of the polymorphic forms, synthesis of the starting material and preparation of the various polymorphic forms.

There is a need in the art for additional pharmaceutical compositions of desloratadine.

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SUMMARY OF THE INVENTION

In one aspect, the present invention provides a pharmaceutical composition of desloratadine comprising of a mixture of crystalline form desloratadine I and II in a weight to weight ratio of about 25% to about 75% of either form to the other and a
20 pharmaceutically acceptable excipient. Some the ratio is approximately 50%.

In another aspect, the present invention provides for a pharmaceutical composition of desloratadine comprising of crystalline form desloratadine I and II in a weight to weight ratio of about 20% to about 40% of Form II and a pharmaceutically acceptable excipient.

25 In another aspect, the present invention provides for a pharmaceutical composition of desloratadine prepared by a process comprising the steps of preparing a mixture of crystalline form desloratadine I and II in a weight to weight ratio of about 20% to about 40% Form II (Or up to 75% each) to Form I and combining the mixture with a pharmaceutically acceptable excipient to obtain a pharmaceutical composition.

30 In another aspect, the present invention provides for a stable mixture of crystalline form desloratadine I and II in a weight to weight ratio of about 25% to about 75% of either form to the other.

In another aspect, the present invention provides for a stable mixture of crystalline form desloratadine in a weight to weight ratio of from about 20-40% Form II to about 60-80% Form I.

In another aspect the present invention provides a stable mixture, and
5 pharmaceutical compositions thereof, of crystalline form desloratadine I and II in a weight to weight ratio of about 25% to about 75% of either form, prepared by a process comprising:

- a) combining desloratadine salt, toluene and a base to obtain a reaction mixture;
- 10 b) heating the mixture, whereby two phases are obtained;
- c) separating the phases;
- d) concentrating the separated organic phase;
- e) dissolving the obtained concentrate in a toluene-2-propanol mixture containing less than about 20% 2-propanol by volume;
- 15 f) cooling the solution to obtain a slurry;
- g) combining the slurry with cold n-heptane; and
- h) recovering mixture of desloratadine forms I and II.

BRIEF DESCRIPTION OF THE FIGURE

- 20 Figure 1 is a stability study of a polymorphic mixture of desloratadine.
Figure 2 is a DSC thermogram of desloratadine Form II after grinding and sieving.
Figure 3 is a DSC thermogram of desloratadine Form I after grinding and sieving.
Figure 4 is a DSC thermogram of a 25:75 mixture of Form I and Form II by weight.
Figure 5 is a DSC thermogram of a 50:50 mixture of Form I and Form II by weight.
25 Figure 6 is a DSC thermogram of a 75:25 mixture of Form I and Form II by weight.
Figure 7 is a DSC thermogram of a 84:16 mixture of Form I and Form II by weight.
Figure 8 is a comparison of X-ray powder diffraction patterns of desloratadine Form I and Form II, and various mixtures thereof.
Figure 9 is similar to figure 8, but illustrates the X-ray diffraction patterns after grinding.
30 Figure 10 is similar to figure 8, but illustrates the X-ray diffraction patterns after storage at 100% relative humidity.
Figure 11 is similar to figure 8, but illustrates the X-ray diffraction patterns after storage at 80% relative humidity.

Figure 12 is similar to figure 8, but illustrates the X-ray diffraction patterns after storage at 60% relative humidity.

DETAILED DESCRIPTION OF THE INVENTION

5 As used herein, the term drying refers to removal of solvent from a solid through application of heat.

The amount of Form I and Form II is expressed herein as a weight ratio relative to each other, *i.e.*, (Form I or II)/Form I plus Form II x 100%.

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In the present invention provides a process suitable for industrial scale for preparation of formulations/compositions of desloratadine. Desloratadine may be crystallized as a mixture of polymorphs in such a way that the ratio between the polymorphs is consistent. As used herein, a "consistent ratio" (or consistent mixture) refers to a ratio of Form I compared to Form II (wt/wt) that is between a range of about $\pm 10\%$ (wt/wt) between lots, as measured by XRPD or FTIR.

15

In one embodiment, the pharmaceutical composition is prepared by using a solution of desloratadine in toluene. The concentration of desloratadine is preferably at least about 15% by weight. A salt of desloratadine may be used as starting material, particularly since salt formation may be used to purify the starting material. A suitable salt is the acetate salt.

20

When starting from a salt, depending on the solubility of the salt, the salt may be suspended in toluene as to form a slurry. A base is then added to the slurry to obtain the free acid, which is readily soluble in toluene, and moves into solution. Suitable bases include those of alkali metal and alkaline earth metals such as potassium, sodium and calcium oxide/hydroxide/carbonate, preferably sodium or potassium hydroxide.

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The base is preferably added as an aqueous solution to the toluene, where two phases form. An about a 2% to about 6% solution of sodium or potassium hydroxide, preferably about a 4% solution may be used. The slurry is preferably heated to increase the reaction

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rate, to for example a temperature of about 40 to about 70°C. The resulting two phase reaction system is preferably stirred at this temperature until complete dissolution.

5 The reaction results in neutralization of the salt, leading to solution of desloratadine free acid in toluene. After phase separation, such as by physical means with use of a separatory funnel, the toluene solution of desloratadine may be washed with distilled water at the same temperature to obtain more of the acid before discarding the aqueous phase.

10 In one embodiment, the resulting toluene solution is concentrated by vacuum or at atmospheric pressure (jacket: preferably about 55°C to about 130°C) to dryness, though it is theoretically possible to precipitate the acid by reducing the solubility of the solvent. The solid material is then dissolved in a mixture of toluene and 2-propanol, in the ratio of about 5:1 to about 15:1, more preferably about 9:1. The addition of relatively minor
15 amounts of 2-propanol (anti-solvent) to toluene manipulates the ratio of Form I and II, and allows for a more facile crystallization. Without 2-propanol, substantially Form II is obtained rather than a mixture.

The mixture is preferably warmed to increase its solubility, such as to a temperature of
20 about 50 to about 70°C, more preferably about 60°C. The warm solution is then preferably cooled to a temperature of about 10°C to about 30°C, more preferably to about 20°C. The cooling may be carried out slowly, during a span of few hours. Cooling in about 4 hours is optimal. After cooling, the resulting slurry is then preferably stirred for a few hours, more preferably of about 5 to about 8 hours.

25 This slurry is preferably warmed again, to about 45 to 55°C, and dropped into cold n-heptane, preferably at about -5 to about +5°C. The precipitated solid material is then recovered preferably by filtration, and may be dried. Drying may be carried out at ambient or reduced pressure. In one embodiment, drying is carried out in a vacuum oven
30 at about 25-35°C overnight.

One skilled in the art may also appreciate that the present invention is not limited by the order of the additions in adding an anti-solvent. For example, a solution may be added to

an anti-solvent or vice versa, though an embodiment may prefer one over the other. Crystallization of a compound is often better when a solution is added to the anti-solvent, but operationally it is often more convenient to add the anti-solvent to the solution. When adding an anti-solvent to a residue, the order of addition is of minimal relevance. The
5 term combining encompasses both orders of addition.

The desloratadine used may be obtained from loratadine, by hydrolysis of the carbamate, preferably under basic conditions. Loratadine itself may be prepared from N-methyl desloratadine by removing N-methyl group of N-methyl desloratadine by formation of the
10 carbamate through reaction with a haloformate. The haloformate used may be an alkyl or aryl formate, with optional halogen substituted at first and/or second position of the formate, *i.e.*, 2-chloroethyl-chloroformate. The carbamate may be prepared in an anhydrous C₅ to C₁₂ hydrocarbon, such as toluene. When N-methyl desloratadine is used as a starting material, loratadine may or may not be isolated in preparation of
15 desloratadine.

The removal of the carbamate group of loratadine may be carried out with a base at elevated temperature. A preferred temperature is reflux temperature. A preferred base is an alkali metal or alkaline earth metal base such as potassium or sodium hydroxide. A
20 preferred solvent is a C₁ to a C₄ alcohol such as 2-propanol.

The desloratadine from the reaction may then be recovered as a polymorphic form. In a preferred embodiment, the reaction mixture is distributed between an organic phase and water, resulting in desloratadine moving to the organic phase. The process described
25 above with toluene may then be used, where a solution of desloratadine in toluene is prepared.

Pharmaceutical formulations of the present invention contain desloratadine Form I and/or Form II, optionally in mixture with other form(s) of desloratadine. The desloratadine
30 prepared by the processes of the present invention are ideal for pharmaceutical composition. In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients. Excipients are added to the composition for a variety of purposes.

Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel[®]), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit[®]), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

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Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel[®]), hydroxypropyl methyl cellulose (e.g. Methocel[®]), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon[®], Plasdone[®]), pregelatinized starch, sodium alginate and starch.

20

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol[®], Primellose[®]), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon[®], Polyplasdone[®]), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrillin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab[®]) and starch.

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Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol and tartaric acid.

Solid and liquid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

In liquid pharmaceutical compositions of the present invention, desloratadine and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the

gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch
5 tragacanth and xanthan gum.

Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar may be added to improve the taste.

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Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid may be added at levels safe for ingestion to improve storage stability.

15 According to the present invention, a liquid composition may also contain a buffer such as guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, sodium lactate, sodium citrate or sodium acetate. Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

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The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable administration in any given case
25 will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories,
30 sachets, troches and lozenges, as well as liquid syrups, suspensions and elixirs.

The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a

hard or soft shell. The shell may be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

The active ingredient and excipients may be formulated into compositions and dosage
5 forms according to methods known in the art.

A composition for tableting or capsule filling may be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the
10 powders to clump into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may then be tableted, or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

A tableting composition may be prepared conventionally by dry blending. For example,
15 the blended composition of the actives and excipients may be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

As an alternative to dry granulation, a blended composition may be compressed directly
20 into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with
25 experience and skill in particular formulation challenges of direct compression tableting.

A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting, however, they are not subjected to a final tableting step.

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Capsules, tablets and lozenges, and other unit dosage forms preferably contain from about 2 to about 20 mg of desloratadine, more preferably about 2 mg to about 10 mg of desloratadine, and most preferably about 5mg.

The compositions of the present invention are substantially physically stable, *i.e.*, substantially stable against polymorphic transformations. The stable compositions may be manufactured in accordance with the acceptable GMP requirements. The stability tests below show the relative stability of the two forms for at least about two months under accelerated conditions. The mixtures of physically stable and undergo less than about 10%, more preferably less than about 5% and most preferably less than about 3% polymorphic change per each polymorph after storage under accelerated ageing conditions (40°C and 75% RH) for at least about 2 months. The mixtures also undergo less than about 10%, more preferably less than about 5% and most preferably less than about 1% polymorphic change in each polymorph when stored for at least about 2 months at room temperature and 60% RH. Additional stability may be imparted by formulating the desloratadine. The pharmaceutical formulation as a mixture may include stable mixtures of about 25% to about 75% weight/weight of one form compared to the other, such as about 25% of Form I, about 50% of Form I and about 75% of Form I, with the rest Form II. In one embodiment, about a 55-65% of Form I and about 35-45% of Form II mixture is used. In another embodiment about 20 to about 40% of Form II is used, more preferably about 24% to about 38%.

The term GMP requirement refers to consistency among batches. The physical properties concerning GMP requirements are stability and solubility. The dissolution rate was not tested due to very low solubility of desloratadine. Nevertheless, the dissolution rate of the stable mixture, when measured by the USP Paddle Method at 50-90 RPM in 900mL water is preferably not less than about 80% by weight of the mixture released after 30 minutes. Preferably, the solubility of the batches is within about a $\pm 10\%$, more preferably within about $\pm 5\%$, and most preferably within about $\pm 1-3\%$ compared to each other.

Stability of desloratadine at relative humidities of 60% 80% and 100% RH, stability under grinding, thermal stability/melting point in the DSC was monitored. The stable mixtures of 25:75, 50:50, 75:25, 84:16 (Form 1:Form 2) do not show any substantial change (Chemical: by degradation; Physical: by transformation to another polymorphic form) in the XRD pattern after exposure at 60%, 80%, 100% RH for one week. Also

those stable mixtures do not show any substantial change in the XRD pattern after grinding for one minute; The sample is ground by hand in a mortar and pestle for about 1 minute. The separate polymorphs (Form I and Form II) were also monitored as a reference, and shown to be stable as well. The mixtures also show a substantial lack in
5 chemical decomposition after storage at 100% humidity for one week and after grinding for 1 minute. This lack of decomposition is preferably undetectable by XRD and NMT 3%, more preferably NMT 2%, and most preferably NMT 3% by weight.

The physical properties of the two separate polymorphs (Form I and Form II) were
10 compared to the physical properties of some mixtures (25:75, 50:50, 75:25, 84:16 Form I:Form II). It was discovered that polymorphic mixtures with different polymorphic compositions have practically invariable physical properties as compared to the separate polymorphs (Form I and Form II). Hence, even if there is polymorphic transformation, the thermal characteristics of the polymorphic mixture may remain substantially the same,
15 which is ideal for formulation.

The thermal stability of the mixtures of polymorphs is comparable to that of the separate polymorphs. The melting temperatures of the stable mixtures, as determined in the DSC, is in the range of 157-158°C, while the separate polymorphs give in the DSC melting
20 temperatures of 156°C and 158°C for Form II and Form I respectively. The similarity in melting points of the separate polymorphs and the stable mixtures indicates that the physical properties are not altered significantly. The DSC curves of the separate polymorphs also do not show any exotherm of decomposition at the temperature above the melting temperature, and also the stable mixtures do not show any event of
25 decomposition above the melting temperature. This lack of decomposition indicates that the mixtures like the separate polymorphs are substantially thermally stable.

A particularly preferred range for the mixture of the present invention is about 20% to about 40% Form II compared to Form I.

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The stable mixtures may be analysed by (FTIR) or X-Ray powder diffraction. Both techniques can be used to monitor polymorphic changes. X-Ray is reported in the literature for its capability to detect generally around 5% polymorphic impurities, but in many cases also to about 1% by weight. With FTIR however, the level of detection is not as accurate.

Instrumentation

X-Ray powder diffraction data were obtained using by method known in the art using a SCINTAG powder X-Ray diffractometer model X'TRA equipped with a solid state detector. Copper radiation of 1.5418 Å was used. A round aluminum sample holder with round zero background quartz plate, with cavity of 25(diameter)*0.5(dept) mm.

DSC analysis was done using a Mettler 821 Star^e. The weight of the samples was about 5 mg; the samples were scanned at a rate of 10°C/min from 30°C to 250°C. The oven was constantly purged with nitrogen gas at a flow rate of 40 ml/min. Standard 40 µl aluminum crucibles covered by lids with 3 holes were used.

IR analysis was done using a Perkin Elmer SPECTRUM ONE FT-IR spectrometer in DRIFT mode. The samples in the 4000-400 cm⁻¹ interval were scanned 64 times with 4.0 cm⁻¹ resolution

In the following examples, the vacuum oven used had a pressure of approximately 30 mm Hg and the refrigerator had a temperature of about 5°C.

EXAMPLE 1

Preparation of desloratadine mixture Form I and Form II

A slurry of desloratadine acetate (20 grams) in toluene (100 ml) and 3.8% KOH solution (95,6 ml) was heated and stirred in the glass reactor at 60 °C until complete dissolution.

After phase separation, toluene solution of desloratadine was washed with distilled water (60 ml) at 60°C. The resulting toluene solution was concentrated by vacuum (jacket: 60°C) to dryness. The solid material was dissolved in toluene-2-propanol 9:1 (74 ml) at 60°C. The warm solution was cooled to 20°C for 4 hours and stirred at this temperature

for 8 hours. This slurry was warmed again to 45°C. In another glass reactor n-heptane (100 ml) was cooled to 0°C. The warm slurry of desloratadine in toluene was dropped into cold n-heptane (temperature of slurry was between 0-12°C), and it was stirred at 0°C for 1 hours. The resulting crystalline product was filtered and dried in a vacuum oven at room temperature. The X-Ray Powder Diffraction showed that the sample had crystallized in as a mixture of polymorphic Form I and Form II (ratio 76 – 24). (13.2 g, 79%, HPLC purity: 99.9 %).

EXAMPLE 2

Preparation of desloratadine mixture Form I and Form II

Desloratadine was prepared from desloratadine acetate according to the example 1. The X-Ray Powder Diffraction showed that the sample had crystallized in as a mixture of polymorphic Form I and Form II (10.8 g, 65%, HPLC purity: 99.8 %). Mixture of Form I and Form II was in the ratio of 42 to 38.

EXAMPLE 3

Preparation of desloratadine mixture Form I and Form II

A slurry of desloratadine acetate (20 grams) in toluene (100 ml) and 3.8% KOH solution (75 ml) was heated and stirred in the glass reactor at 60 °C until complete dissolution.

After phase separation, toluene solution of desloratadine was washed with distilled water (60 ml) at 60°C. The resulting toluene solution was concentrated by vacuum (jacket: 60°C) to dryness. The solid material was dissolved in toluene-2-propanol 9:1 (50 ml) at 60°C. The warm solution was cooled to 20°C for 4 hours and stirred at this temperature for 10 hours. This slurry was warmed again to 50°C. The resulting toluene slurry was concentrated by vacuum (jacket: 50°C) to half of volume. In another glass reactor n-heptane (100 ml) was cooled to 0°C. The warm slurry of desloratadine in toluene was dropped into cold n-heptane (temperature of slurry was between 0-12°C), and it was stirred at 0°C for 1 hours. The resulting crystalline product was filtered and was dried in a vacuum oven at room temperature. The X-Ray Powder Diffraction showed that the sample had crystallized in as a mixture of polymorphic Form I and Form II (64 to 36%) (10.6 g, 63%) HPLC purity: 99.7 %.

Study of Stability of Desloratadine Polymorphs

The desired mixture of polymorphic forms (Form 1 and Form 2) of desloratadine was prepared by different methods in order to investigate a stability of polymorphic ratio of desloratadine. Stability of ratio of the mixture of desloratadine polymorphic forms at two different conditions:

- 5 1.) 25°C, 60 % RH
- 2.) 40°C, 75 % RH

In all cases samples were packed in polyethylene and store above conditions.

Example 1 of stability tests:

- 10 Recrystallization of desloratadine (3 g) from dimethyl carbonate–diethyl carbonate (1:1) (35 ml) at 110°C obtained a mixture. The X-ray Powder Diffraction measurement showed that the ratio of the two polymorphic forms was 57:43 (Form 1/Form 2).

		25 °C 60% RH		40 °C 75% RH	
Time	Time (weeks)	Form 1 (%)	Form 2 (%)	Form 1 (%)	Form 2 (%)
0 week	0	57	43	57	43
1 week	1	59	41	46	54
2 weeks	2	53	47	43	57
1 month	4	55	45	50	50
2 months	8	63	37	39	61
3 months	12	52	48		

- 15 Stability study is disclosed in Figure 1.

Example 2 of Stability Tests:

Recrystallization of desloratadine (3 g) from iso-propanol–n-heptane (1:1) (11 ml) at 85 °C obtained a mixture. The X-ray Powder Diffraction measurement showed that the ratio of the two polymorphic forms was 62:38 (Form 1/Form 2).

- 20 of the two polymorphic forms was 62:38 (Form 1/Form 2).

		25 °C, 60% RH		40 °C, 75% RH	
Time	Time (weeks)	Form 1 (%)	Form 2 (%)	Form 1 (%)	Form 2 (%)
0 week	0	62	38	62	38
1 week	1	65	35	63	37
2 weeks	2	61	39	64	36
1 month	4	66	34	65	35
2 months	8	67	33	65	35
3 months	12	66	34		

Example 3 of Stability Tests:

Recrystallization of desloratadine (10 g) from iso-propanol (25 ml) at 80 °C. The cooling term was regulated. The temperature was cooled to 0°C in 30 min, which generated a mixture. The X-ray Powder Diffraction measurement showed that the ratio of the two polymorphic forms was 74:26 (Form 1/Form 2).

		25 °C, 60% RH		40 °C, 75% RH	
Time	Time (weeks)	Form 1 (%)	Form 2 (%)	Form 1 (%)	Form 2 (%)
0 week	0	74	26	74	26
1 week	1	79	21	77	23
2 weeks	2	74	26	81	19
1 month	4	79	21	78	22
2 months	8	75	25	78	22
3 months	12	74	26	75	25
6 months	24	77	23	75	25

Example 4 of Stability Tests:

Recrystallization of desloratadine (10 g) from iso-propanol (25 ml) at 80 °C. The solution was seeded with Form II. The cooling term was regulated. The temperature was allowed to 0 °C in 30 minutes. The X-ray Powder Diffraction measurement showed that the ratio of the two polymorphic forms was 76:24 (Form 1/Form 2).

		25 °C, 60% RH		40 °C, 75% RH	
Time	Time (weeks)	Form 1 (%)	Form 2 (%)	Form 1 (%)	Form 2 (%)
0 week	0	76	24	76	24
1 week	1	87	13	76	24
2 weeks	2	80	20	82	18
1 month	4	82	18	88	12
2 months	8	86	14	85	15
3 months	12	81	19	82	18
6 months	24	84	16	82	18

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art would appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to, limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in

numerous publications. Polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Sciences, Volume 95 may be used as a guidance. All references mentioned herein are incorporated in their entirety.

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What is claimed is:

1. A pharmaceutical composition of desloratadine comprising of a mixture of crystalline form desloratadine I and II in a weight to weight ratio of about 25% to about 75% of either form to the other and a pharmaceutically acceptable excipient.
- 5 2. The pharmaceutical composition of claim 1, wherein the ratio is approximately 50%.
3. The pharmaceutical composition of claim 1, wherein the ratio is of about 55 to about 65% Form I to about 35 to about 45% of Form II.
4. A pharmaceutical composition of desloratadine comprising of crystalline form
10 desloratadine I and II in a weight to weight ratio of about 20% to about 40% of Form II and a pharmaceutically acceptable excipient.
5. The pharmaceutical composition of claim 4, wherein the Form II content of the mixture is about 24% to about 38%.
6. A pharmaceutical composition of desloratadine prepared by a process comprising
15 the steps of:
 - a) preparing a mixture of crystalline form desloratadine I and II in a weight to weight ratio of about 20% to about 40% Form II to Form I; and
 - b) combining the mixture with a pharmaceutically acceptable excipient to obtain a pharmaceutical composition.
- 20 7. The pharmaceutical composition of claim 1, 2, 3, 4, 5 or 6, wherein the mixture used for composition has a melting temperature of about 157°C to about 158°C as measured by DSC.
8. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6 or 7, wherein the mixture used for composition undergoes less than about 1% by weight polymorphic change and
25 chemical degradation after grinding for one minute.
9. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7 or 8, wherein the mixture used for composition undergoes less than about 1% by weight chemical decomposition after storage at 100% relative humidity for one week.
10. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, 8 or 9, wherein the
30 mixture used for composition undergoes less than about 10% polymorphic change for each polymorph after storage for 2 months at 40°C at 75% RH.

11. The pharmaceutical composition of claim 10, wherein the mixture used for composition undergoes less than about 5% polymorphic change for each polymorph after storage for 2 months at 40°C at 75% RH.
12. The pharmaceutical composition of claim 11, wherein the mixture used for
5 composition undergoes less than about 3% polymorphic change for each polymorph after storage for 2 months at 40°C at 75% RH.
13. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, wherein the mixture used for composition undergoes less than about 10% polymorphic change for each polymorph after storage for 2 months at room temperature at 60% RH.
- 10 14. The pharmaceutical composition of claim 13, wherein the mixture used for composition undergoes less than about 5% polymorphic change for each polymorph after storage for 2 months at room temperature at 60% RH.
15. The pharmaceutical composition of claim 14, wherein the mixture used for composition undergoes less than about 1% polymorphic change for each polymorph after
15 storage for 2 months at room temperature at 60% RH.
16. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15, wherein the mixture used for formulation complies with the GMP requirements.
17. A method of preventing or treating allergenic reactions in a mammal comprising administering the pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12,
20 13, 14, 15 or 16 to the mammal in need thereof.
18. A stable mixture of crystalline form desloratadine I and II in a weight to weight ratio of about 25% to about 75% of either form to the other.
19. A stable mixture of crystalline form desloratadine in a weight to weight ratio of from about 20-40% Form II to about 60-80% Form I.
- 25 20. The stable mixture of claim 19, wherein the weight to weight ratio is from about 24-38% Form II to about 62-76% form I.
21. A stable mixture of crystalline form desloratadine I and II in a weight to weight ratio of about 25% to about 75% of either form, prepared by a process comprising:
- i) combining desloratadine salt, toluene and a base to obtain a reaction mixture;
 - 30 j) heating the mixture, whereby two phases are obtained;
 - k) separating the phases;
 - l) concentrating the separated organic phase;

- m) dissolving the obtained concentrate in a toluene-2-propanol mixture containing less than about 20% 2-propanol by volume;
 - n) cooling the solution to obtain a slurry;
 - o) combining the slurry with cold n-heptane; and
 - 5 p) recovering mixture of desloratadine forms I and II.
22. The stable mixture of claim 21, wherein the process further comprises washing the product of step c with water.
23. The stable mixture of claim 21, wherein the process further comprises warming the product of step f to about 45°C.
- 10 24. The stable mixture of any of claims 18, 19, 20, 21, 22 or 23 having a melting point in the range of about 157°C to about 158°C.
25. The stable mixture of claim 18, 19, 20, 21, 22, 23 or 24 wherein the mixture is stable in that it undergoes less than about 10% polymorphic change for each polymorph after storage for 2 months at 40°C at 75% RH.
- 15 26. The stable mixture of claim 25, wherein the mixture undergoes less than about 5% polymorphic change for each polymorph after storage for 2 months at 40°C at 75% RH.
27. The stable mixture of claim 26, wherein the mixture undergoes less than about 3% polymorphic change for each polymorph after storage for 2 months at 40°C at 75% RH.
28. The stable mixture of any of claims 18, 19, 20, 21, 22, 23 24, 25, 26 or 27,
- 20 wherein the mixture undergoes less than about 10% polymorphic change for each polymorph after storage for 2 months at room temperature at 60% RH.
29. The stable mixture of claim 28, wherein the mixture undergoes less than about 5% polymorphic change for each polymorph after storage for 2 months at room temperature at 60% RH.
- 25 30. The stable mixture of claim 29, wherein the mixture undergoes less than about 1% polymorphic change for each polymorph after storage for 2 months at room temperature at 60% RH.
31. The stable mixture of any of claim 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, wherein the mixture complies with the GMP requirements.
- 30 32. The stable mixture of any of claims 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or 31, wherein the dissolution rate in vitro of the stable mixture, when measured by the U.S.P Paddle Method at 50-90 RPM in 900mL water is not less than 80% (by weight) of the mixture released after 30 minutes.

33. A pharmaceutical formulation comprising the stable mixture of claim 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 or 32.

34. A method of preventing or treating allergenic reactions in a mammal comprising administering the pharmaceutical composition of claim 18, 19, 20, 21, 22, 23, 24, 25, 26,
5 27, 28, 29, 30, 31, 32 or 33 to the mammal in need thereof.

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Figure 1

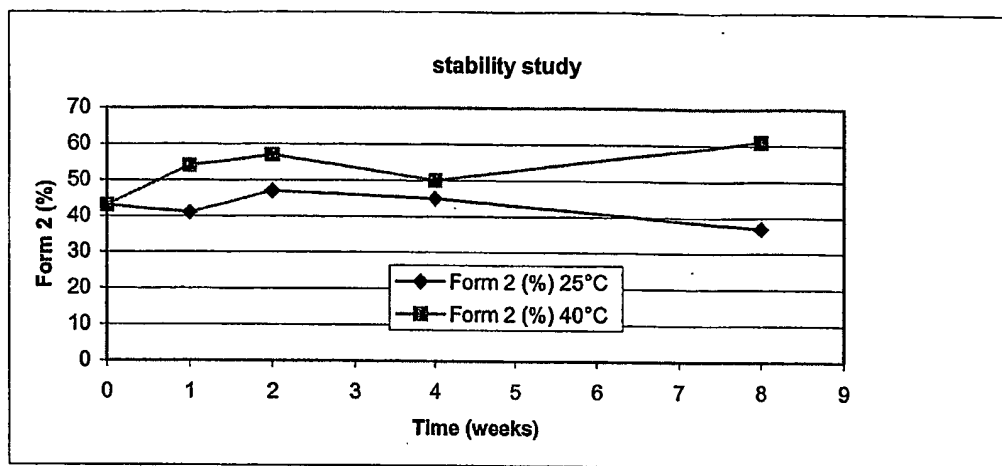


FIG. 2

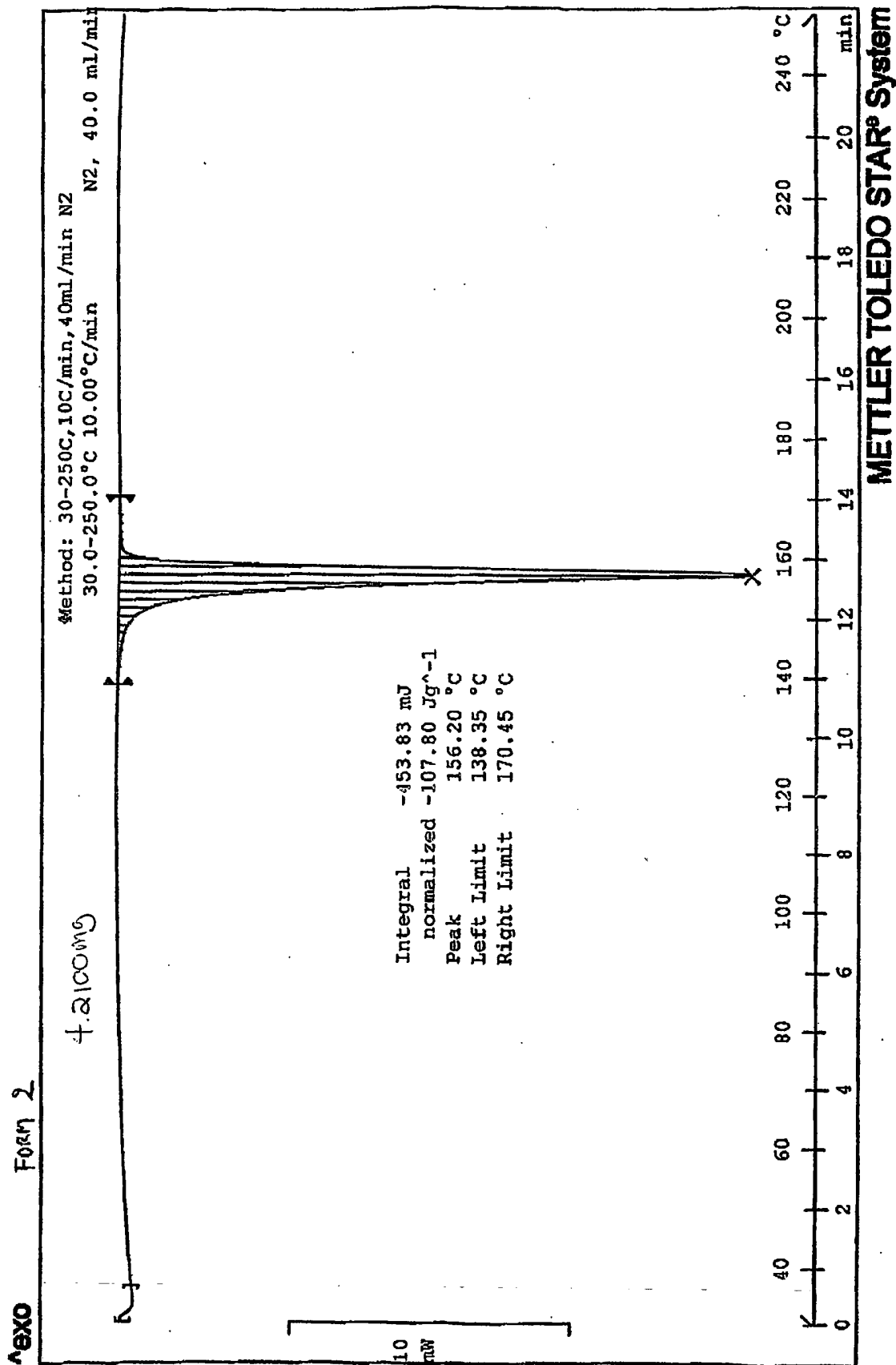
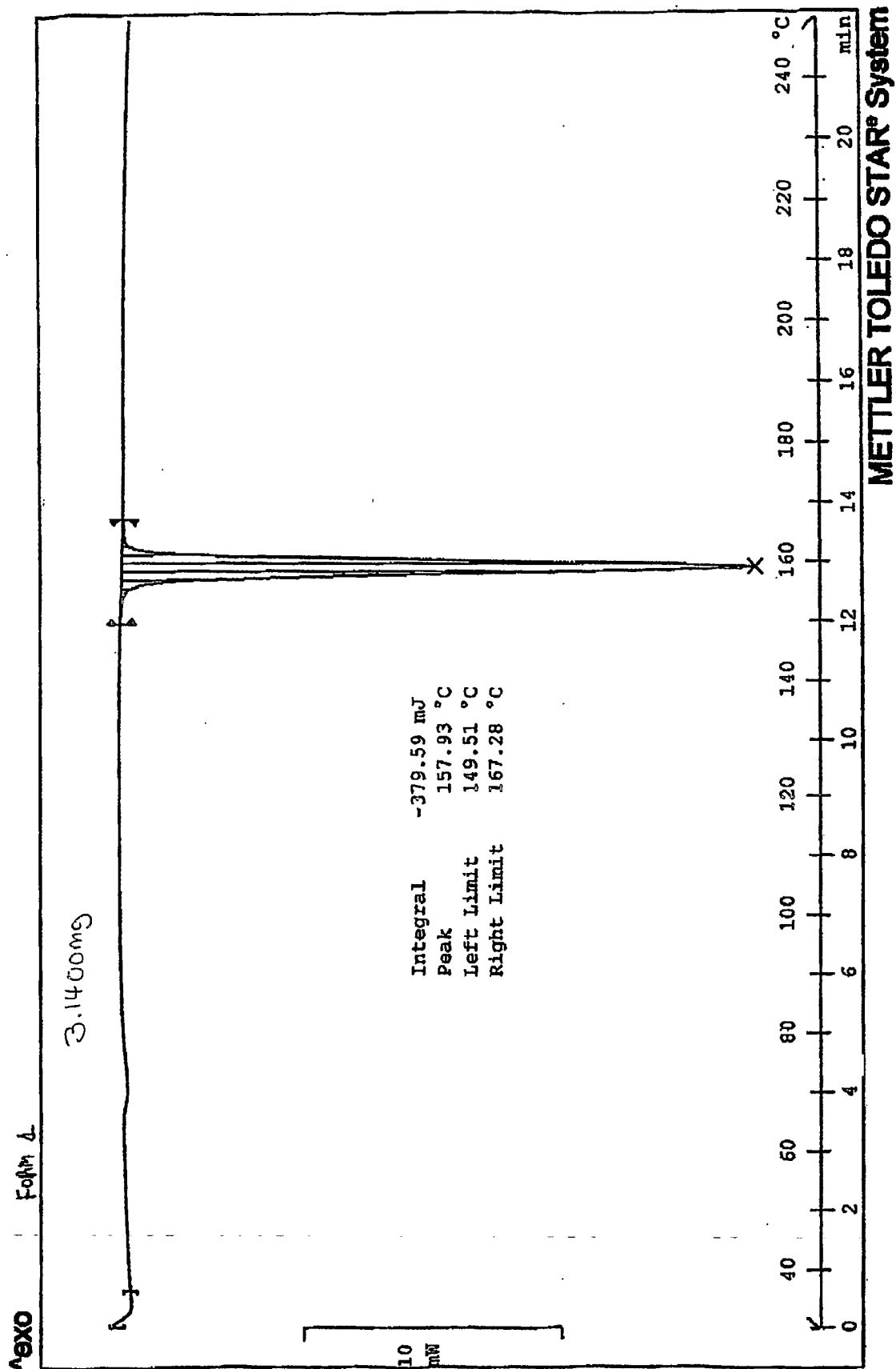


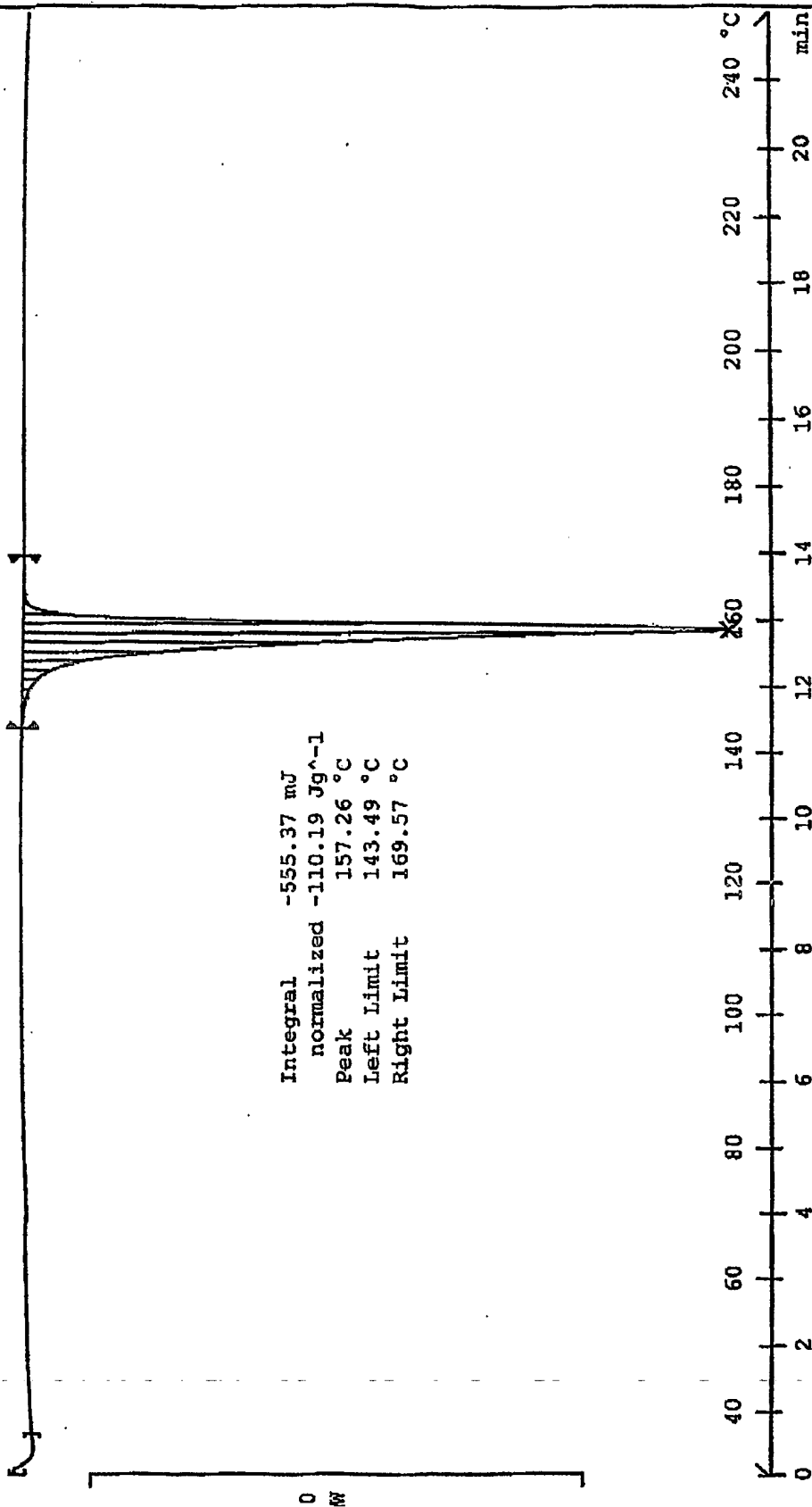
FIG. 3



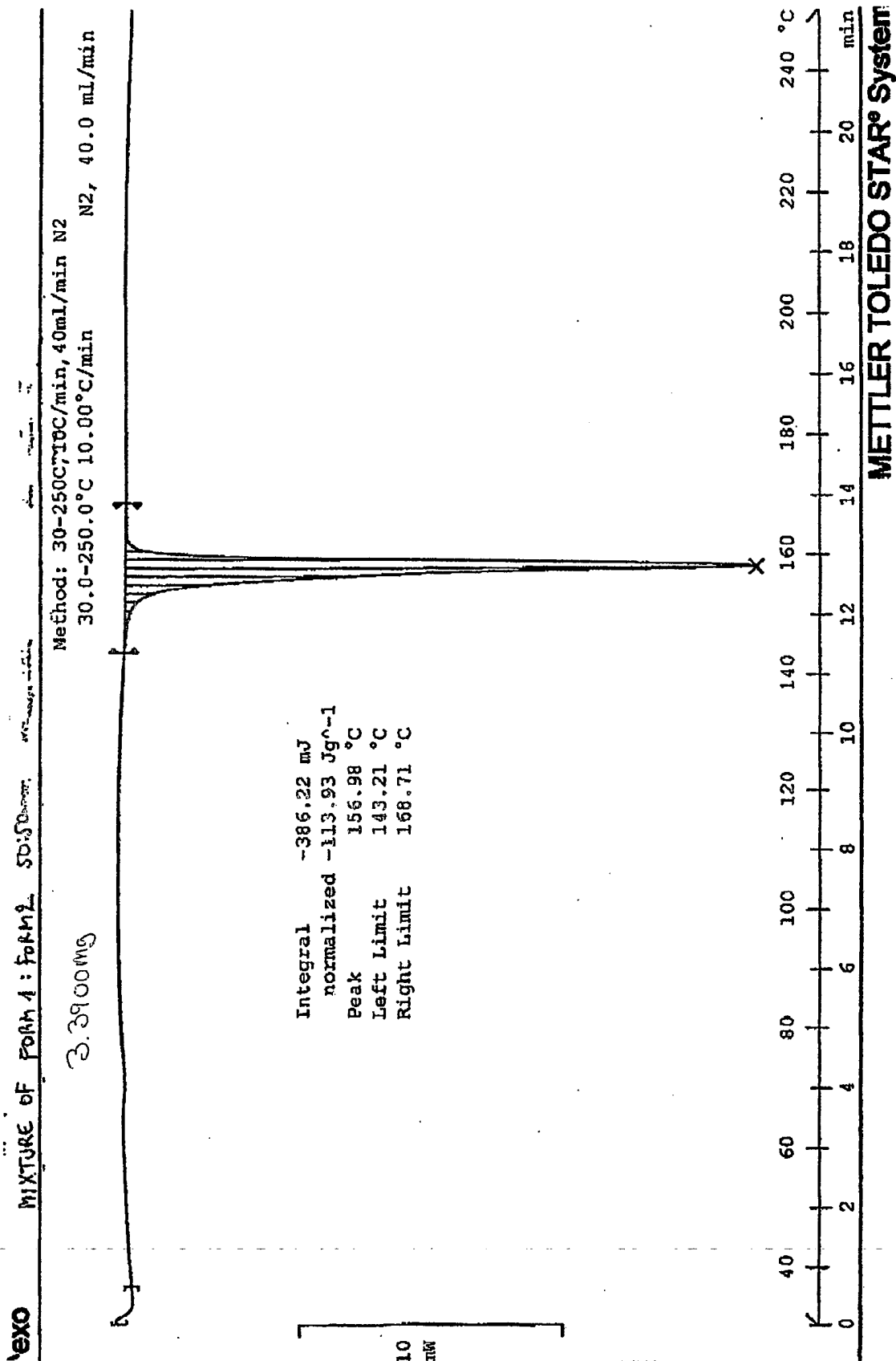
exo MIXTURE OF FORM 1: FORM 2 25:75

5.0400mg

Method: 30-250C, 10C/min, 40ml/min N2
30.0-250.0°C 10.00°C/min N2, 40.0 ml/min



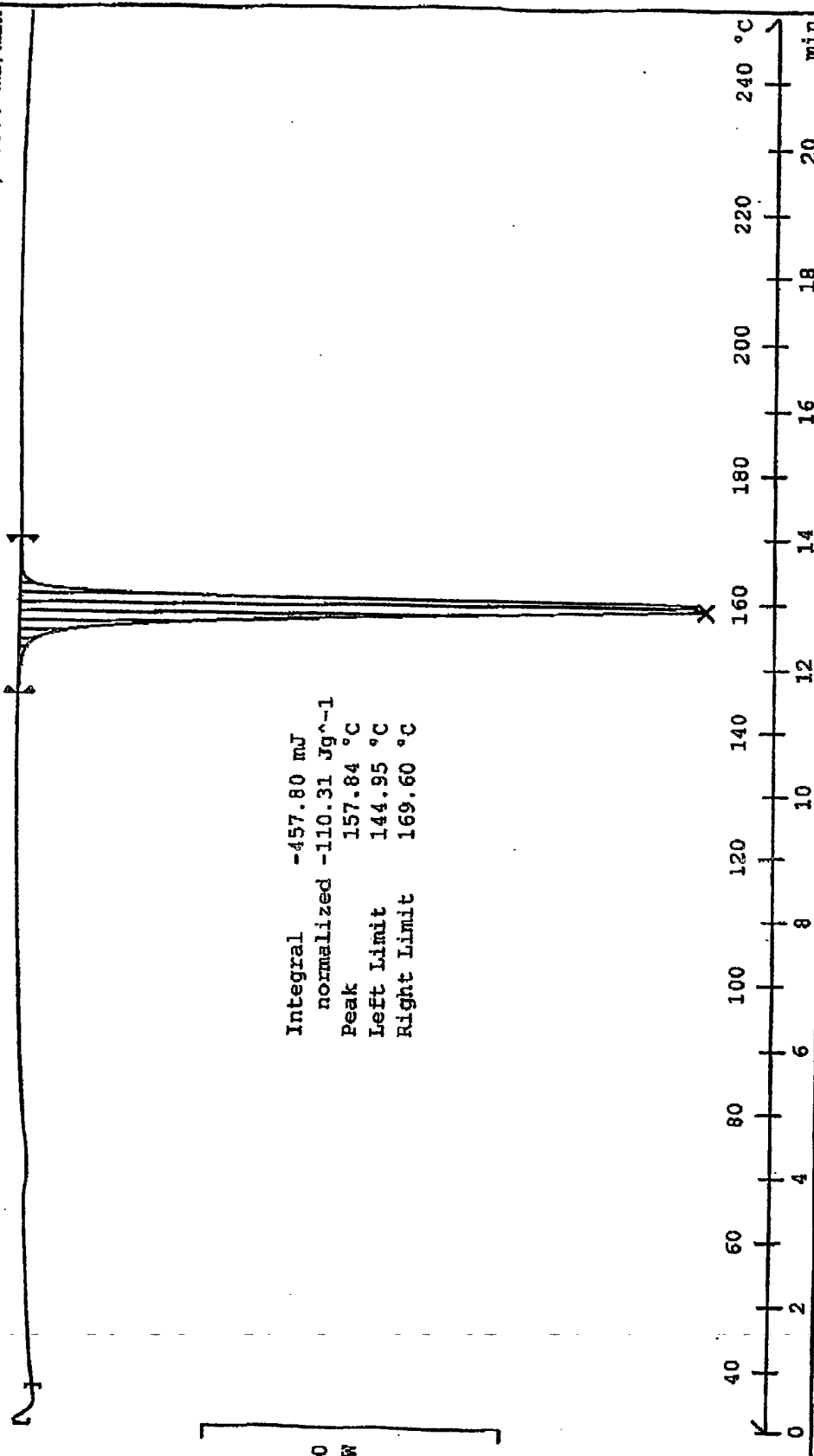
METTLER TOLEDO STAR® System



exo MIXTURE OF FORM 4: FORM 2 75:25

4.1500mg

Method: 30-250C, 10C/min, 40mL/min N2
30.0-250.0°C 10.00°C/min N2, 40.0 mL/min

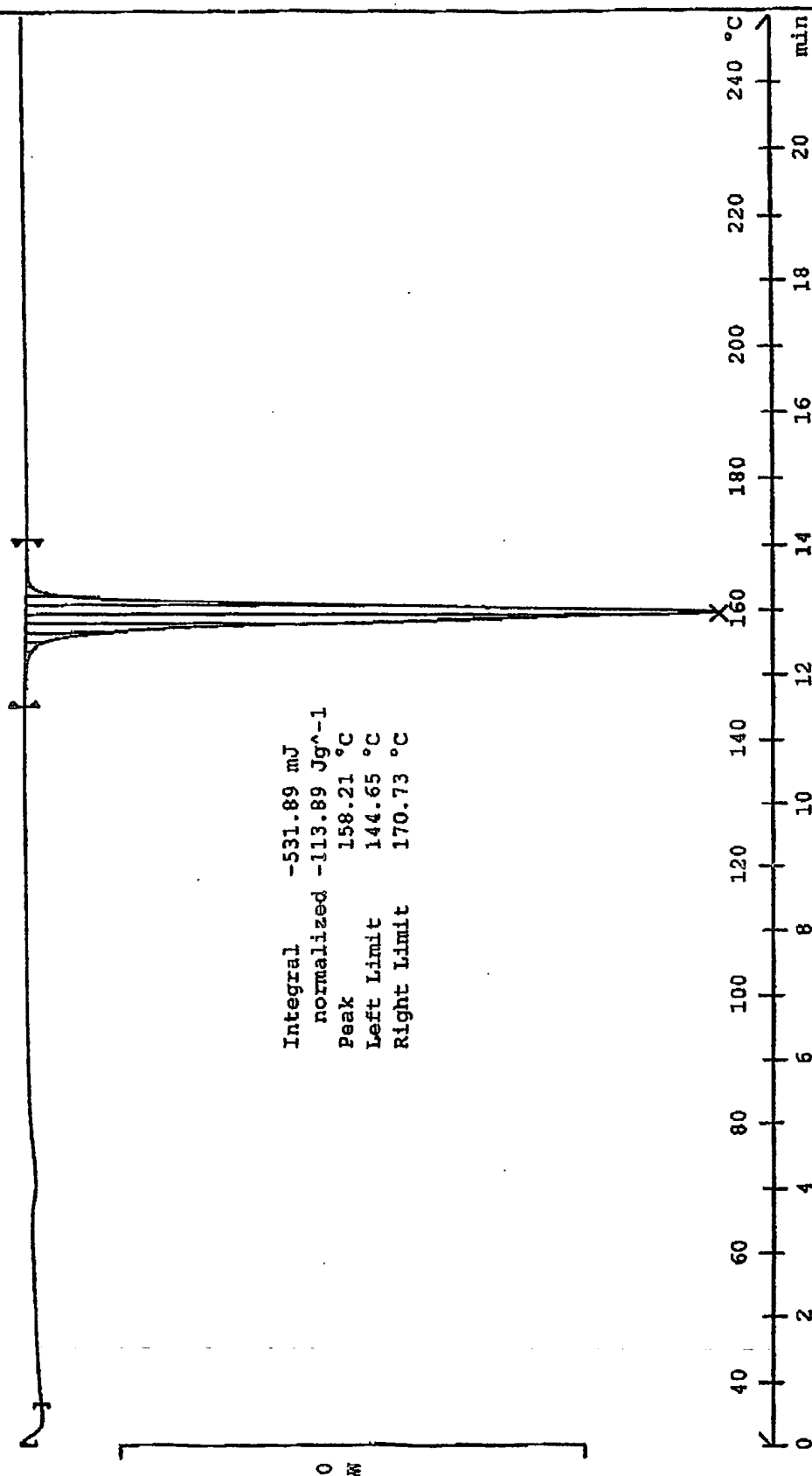


METTLER TOLEDO STAR® System

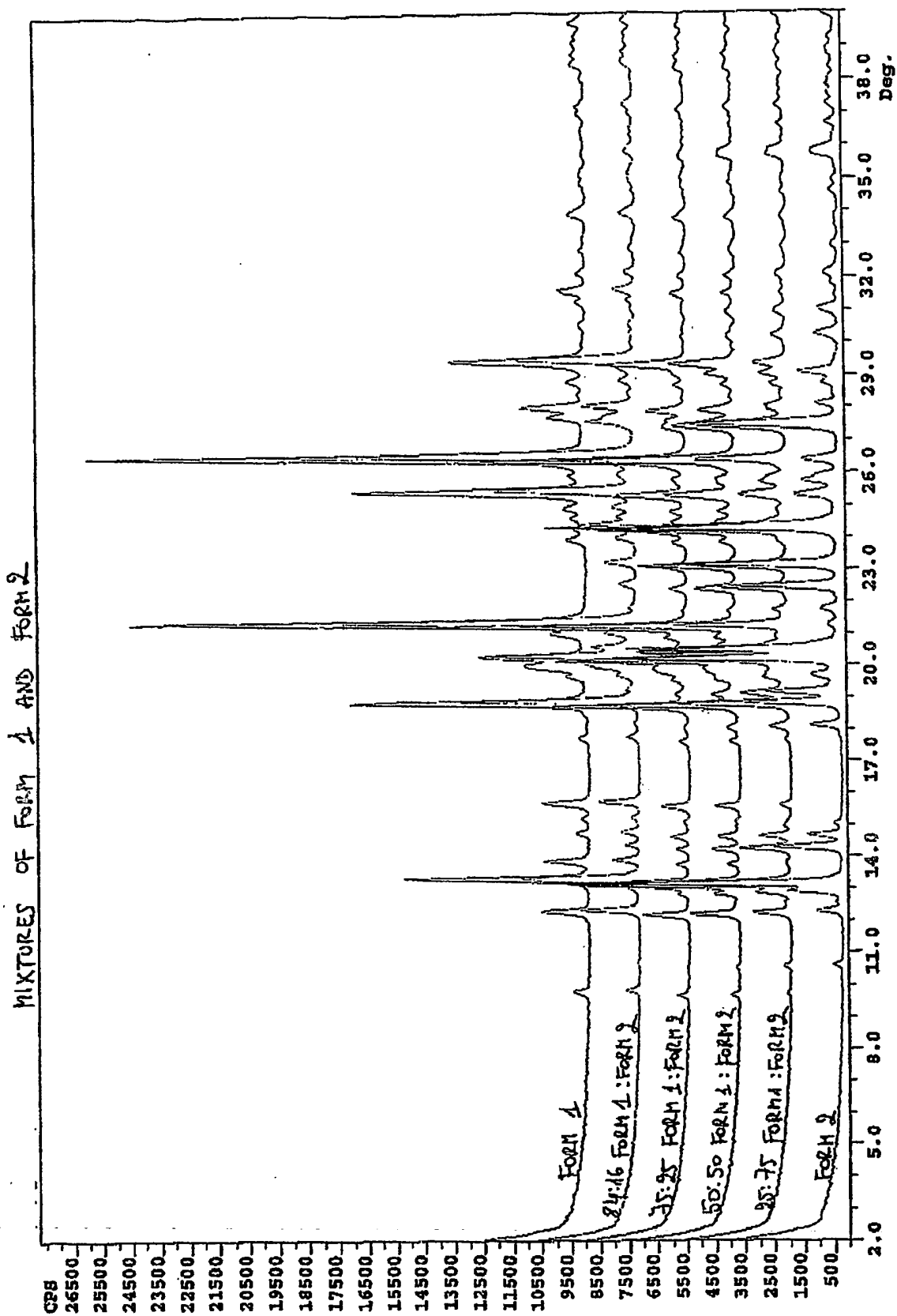
BXO MIXTURE OF FORM 1: Form 2 84:16

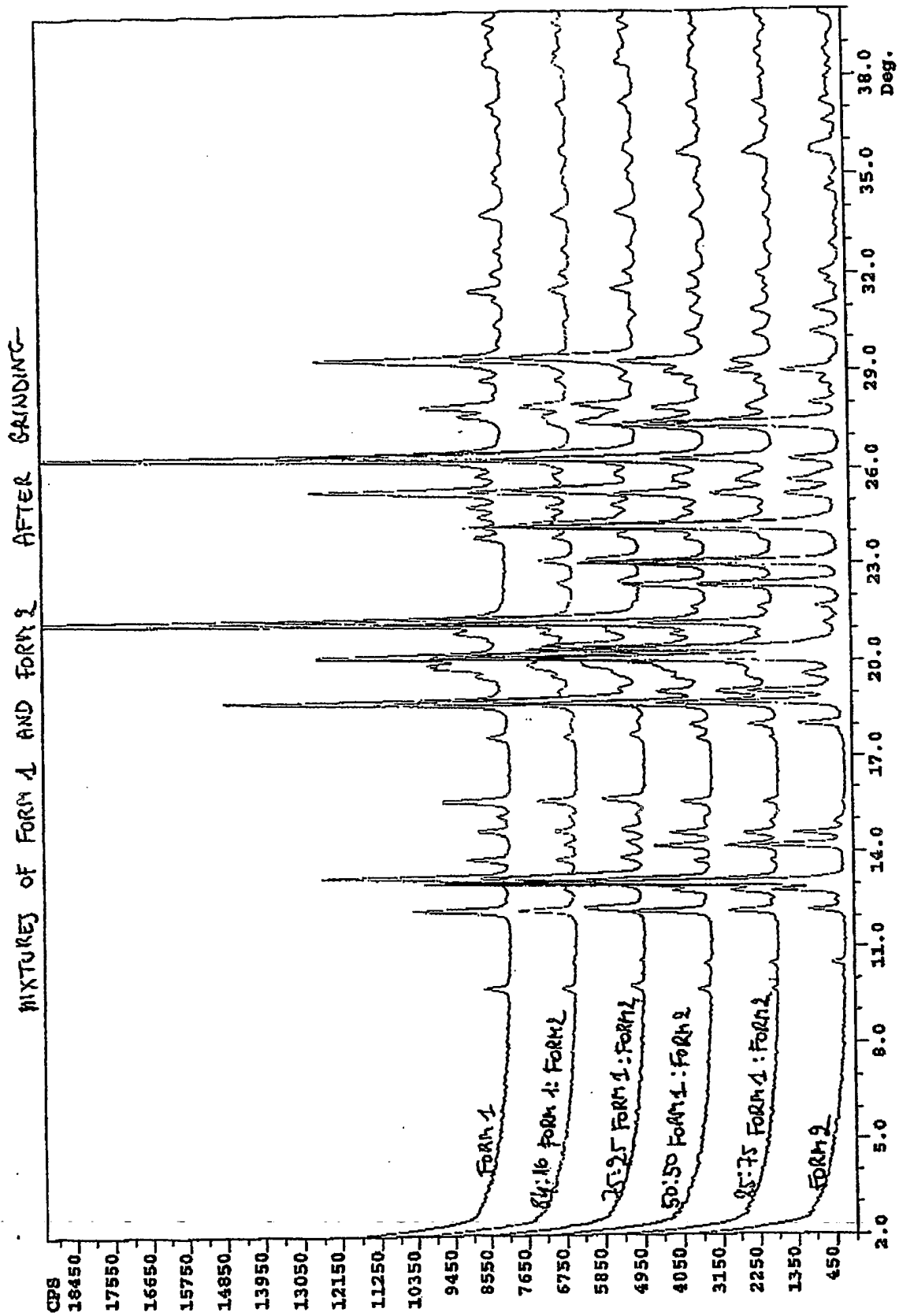
Method: 30-250°C, 10°C/min, 40ml/min N2
30.0-250.0°C 10.00°C/min N2, 40.0 ml/min

4.6700mg

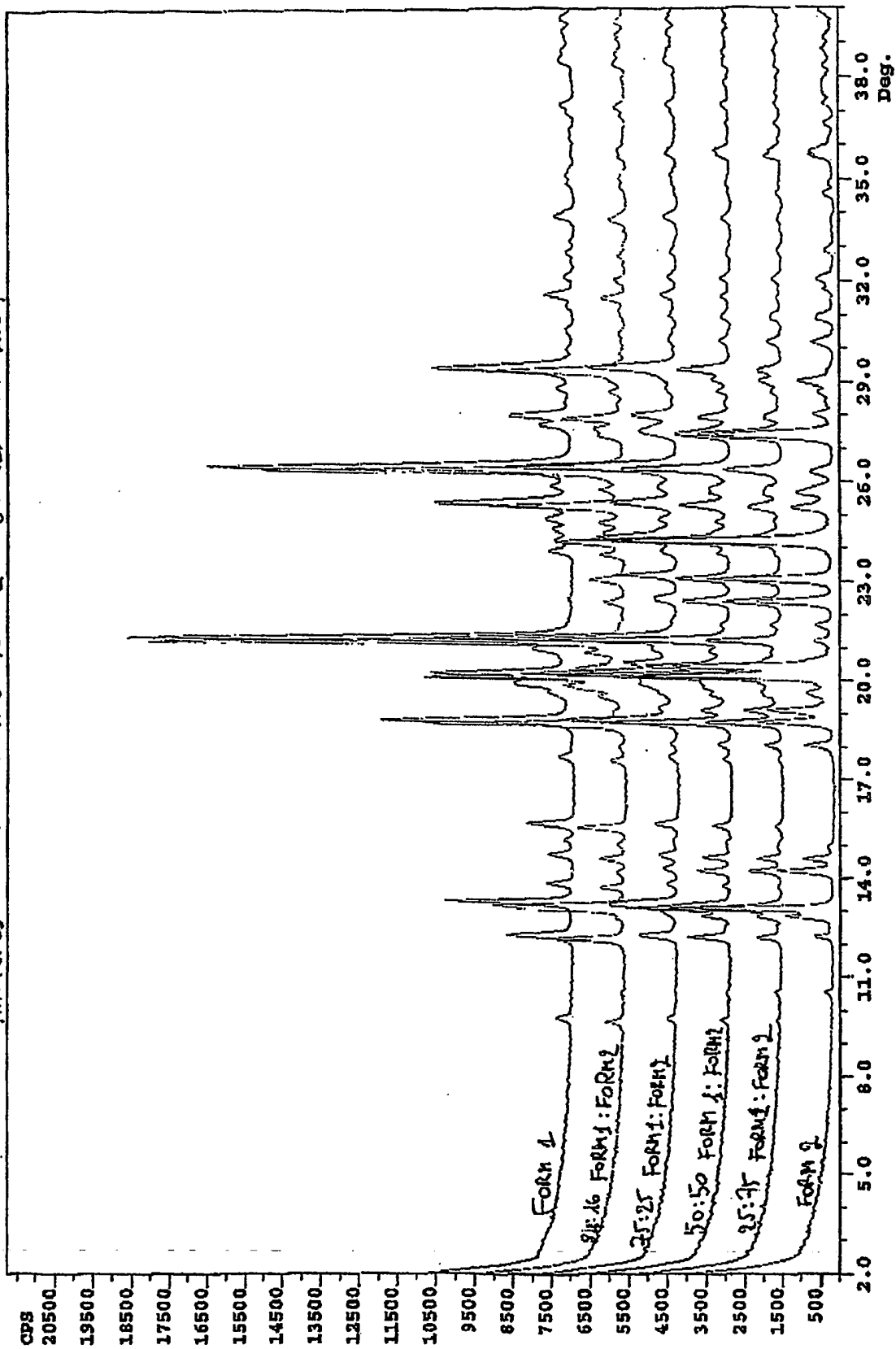


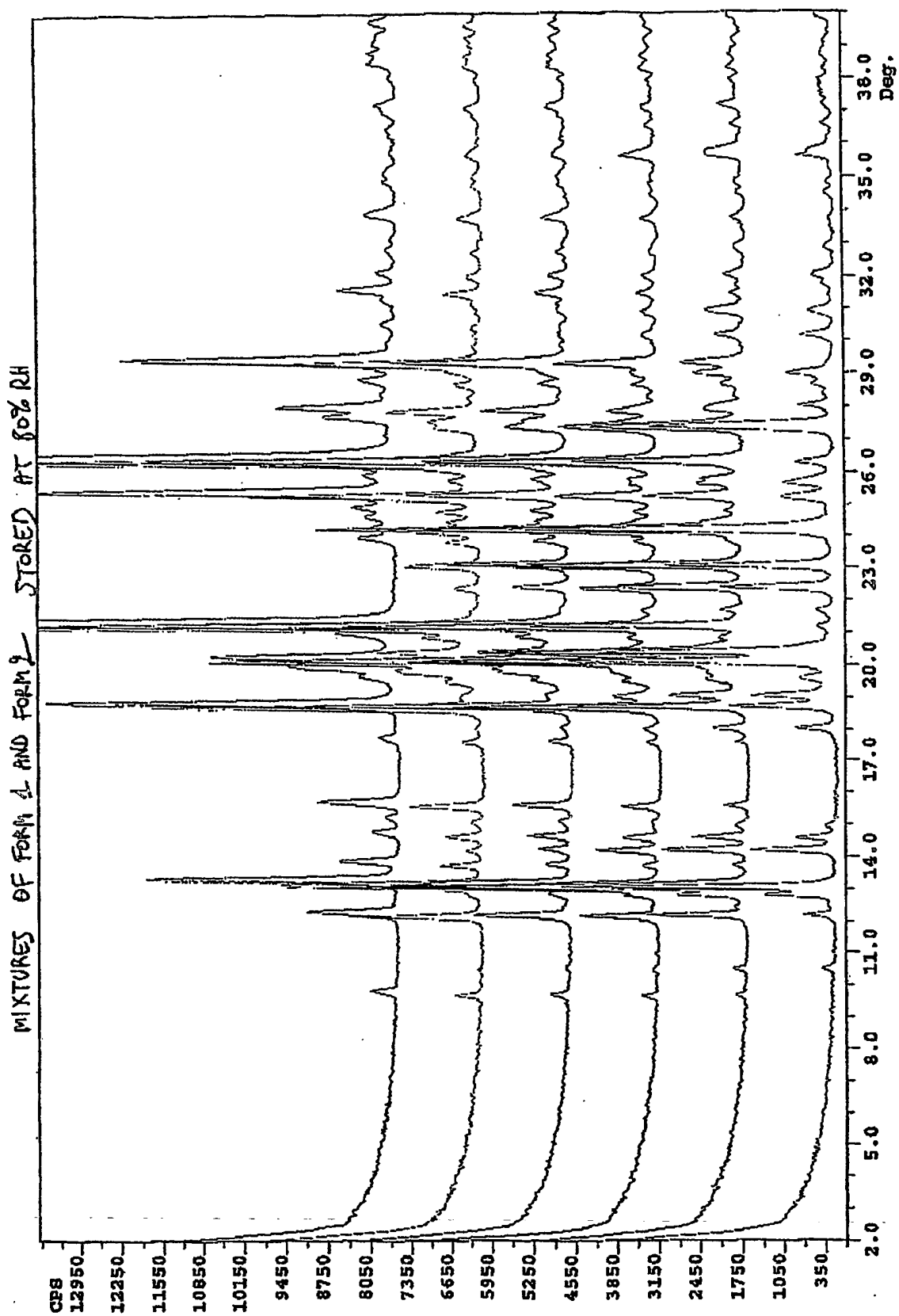
METTLER TOLEDO STAR® System

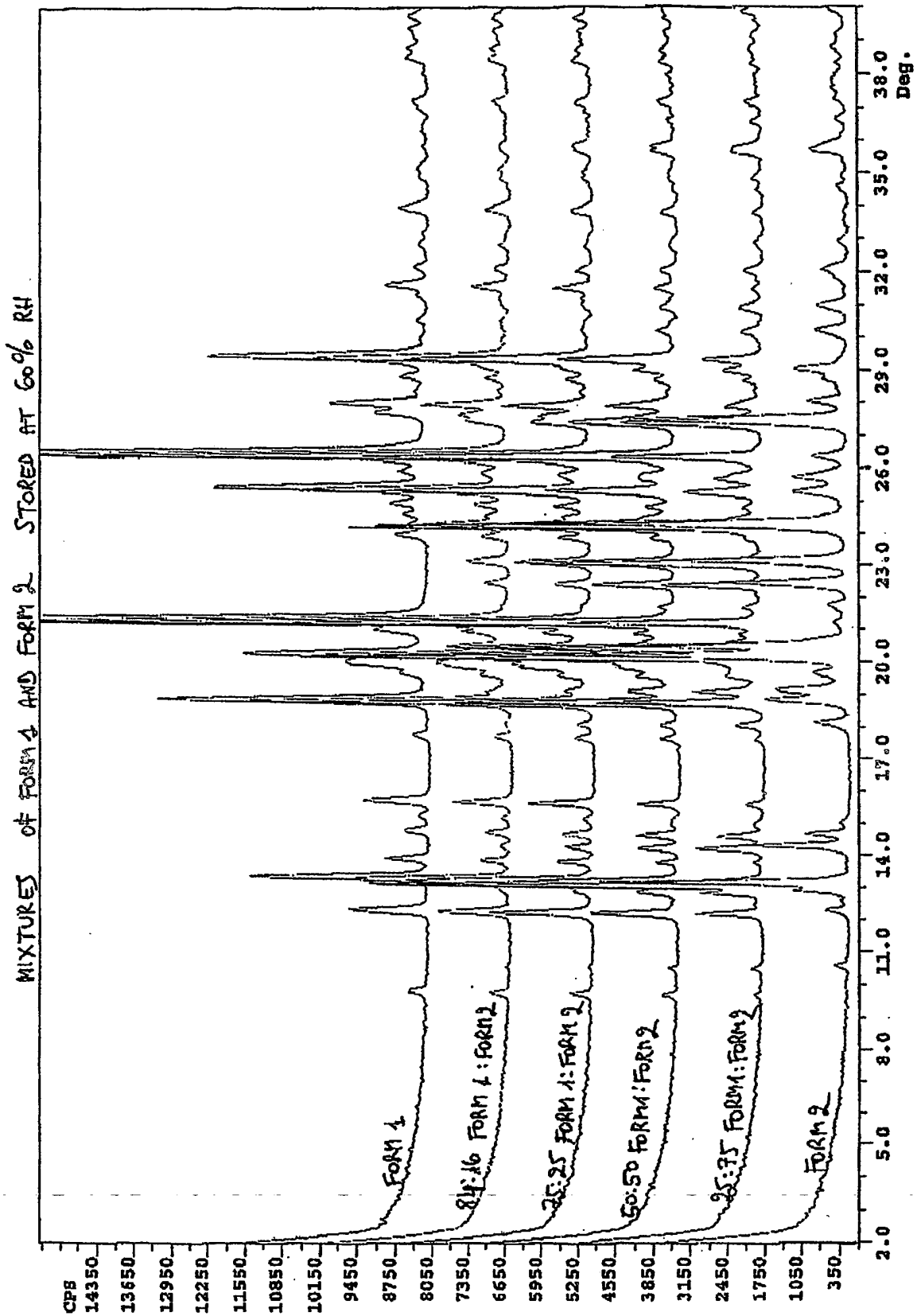




MIXTURES OF FORM 1 AND FORM 2 STORED AT 100%







(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
23 September 2004 (23.09.2004)

PCT

(10) International Publication Number
WO 2004/080461 A3

- (51) International Patent Classification⁷: **A61K 31/4545**, A61P 37/06 (74) Agents: **BRAINARD, Charles, R. et al.**; Kenyon & Kenyon, One Broadway, New York, NY 10004-1050 (US).
- (21) International Application Number: PCT/US2004/007723
- (22) International Filing Date: 12 March 2004 (12.03.2004) -
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/454,299 12 March 2003 (12.03.2003) US
60/515,354 28 October 2003 (28.10.2003) US
60/516,904 3 November 2003 (03.11.2003) US
60/526,339 1 December 2003 (01.12.2003) US
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report: 28 October 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/080461 A3

(54) Title: STABLE PHARMACEUTICAL COMPOSITIONS OF DESLORATADINE

(57) Abstract: Provided is a stable pharmaceutical composition of desloratadine.

INTERNATIONAL SEARCH REPORT

International Application No
US2004/007723

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4545 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS, EMBASE, MEDLINE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/01450 A (SCHERING CORP) 14 January 1999 (1999-01-14) page 5, paragraph 2 - page 6, paragraph 2 page 15, paragraph 3 -----	1,4, 6-19, 21-34
X	US 6 506 767 B1 (ECKHART CHARLES G ET AL) 14 January 2003 (2003-01-14) column 1, line 45 - column 2, line 55 column 9, line 55 - line 61 claims 7-10 column 3, line 52 - line 66 -----	1,4, 6-19, 21-34
A	US 4 659 716 A (VILLANI FRANK J ET AL) 21 April 1987 (1987-04-21) examples V,VI example III ----- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

9 September 2004

17/09/2004

Name and mailing address of the ISA

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Authorized officer

Bonzano, C

INTERNATIONAL SEARCH REPORT

International Application No
T/US2004/007723

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 270 818 A (SCHERING CORP) 15 June 1988 (1988-06-15) page 59, paragraph G page 71, paragraph E page 81; example 7 -----	
A	WO 95/10515 A (SCHERING CORP) 20 April 1995 (1995-04-20) page 57, paragraph G -----	
P,A	WO 03/086275 A (CHITTURI TRINADHA RAO ; THENNATI RAJAMANNAR (IN); UNNAM RAJA SEKHAR (I) 23 October 2003 (2003-10-23) page 9; example 1 -----	
P,A	WO 2004/012738 A (PATEL HIREN V ; RAY ANUP KUMAR (US); GENEVA PHARMACEUTICALS INC (US);) 12 February 2004 (2004-02-12) page 2, paragraph 6 -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/007723

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17,34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PT/US2004/007723

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9901450	A	14-01-1999	AT 239010 T	15-05-2003
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